Patterns of Failure Following Surgical Resection of Colorectal Cancer Liver Metastases

Rationale for a Multimodal Approach

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A total of 45 patients, after surgical resection of colorectal liver cancer metastases, were retrospectively analyzed to define areas of failure, to identify some possible prognostic factors (site of primary, stage, site, number of metastases, preoperative carcinoembryonic antigen, differentiation of the primary, type of surgery), and to seek a new rationale for a multimodal approach. The median postoperative follow-up was 18 months (range: 4–45 months). Survival rate was calculated by the actuarial method, and statistical significance was tested by the Mantel-Haenszel test. Twenty-eight patients had a relapse. These recurrences were hepatic in 11 patients, extrahepatic (intra- and extra-abdominal) in 12 patients, and intra- and extrahepatic in five patients: The stage (classification of the Istituto Nazionale Tumori of Milan) was the most important parameter related to the overall recurrence rate (47% in stage I, 62% in stage II, and 81% in stage III) and to the overall and disease-free survival. Stage was significantly related to hepatic relapse but not to extrahepatic relapse. In stage I the failure rate of 18 months was similar in hepatic and extrahepatic relapses (one third to one fourth of the patients); in stages II and III the hepatic failure rate was always higher than the extrahepatic rate. These data indicate that surgery alone is an inadequate form of therapy in cases of colorectal cancer metastases of the liver, and an adjuvant therapy, including alternate regimens of intraperitoneal and systemic chemotherapy, should be considered.

ALTHOUGH SURGICAL RESECTION of hepatic metastases from colorectal cancer has gained worldwide acceptance as a therapeutic approach in selected cases, and several reports deal with more than 20 cases from individual institutions,[1–15] there is little information available[1,13,16–18] on the natural history of the resected cases and the areas of failure after hepatic resection. More data regarding the natural history of these cases could help the oncologic surgeon in the identification of patients at high risk for recurrences and could aid in the planning of a multimodal approach in selected cases.

We thus evaluated the recurrence rate and the areas of failure after curative liver resection for metastatic colorectal cancer in a series of 45 consecutive patients.

TABLE 1. *Main Characteristics of the Series*

	No. of Patients	Median Age (Range) (Years)
Sex		
Male	18	52 (33–75)
Female	27	53 (36–68)
Diagnosis		
Synchronous	12	
Metachronous	33	
Primary location		
Rectum and sigmoid colon	31	
Left colon	8	
Transverse colon	2	
Right colon	4	
Dukes' classification		
B	14	
C	21	
Unknown	10*	
Differentiation of primary tumor		
Well differentiated	3	
Intermediate differentiation	19	
Poorly differentiated	6	
Unknown	17*	

* Primary resected elsewhere.

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TABLE 2. *Case Distribution According to the Classification of Hepatic Metastases*[19]

Category	Single	Multiple (at One Lobe)	Bilateral	Total
H_1 (<25%)	21	4	2	27
H_2 (25–50%)	2	7	1	10
H_3 (>50%)	3	3	2	8
Total	26	14	5	45

TABLE 3. *Distribution of Surgical Resections by Stage and Category*

Type of Surgery	Stage I Category H_1s	Stage II Category H_1m-H_1b-H_2s	Stage III Category H_2m-H_2b, H_3s-H_3m-H_3b	Total
Right lobectomy	2	2	13	17
Extended right lobectomy	—	2	1	3
Left lobectomy	1	—	—	1
Left lateral lobectomy	5	—	1	6
Sublobectomy	13	4	1	18
Total	21	8	16	45

Patients and Methods

From May 1980 to October 1984, 45 patients admitted to the Istituto Nazionale Tumori of Milan had successful radical liver surgery for metastases confined to the liver, after a previously resected colorectal cancer. Table 1 reports the main characteristics of the patients. In 12 patients the metastases were synchronous, and in 33 patients they were diagnosed after a mean of 22 months (range: 3–60 months) from primary tumor resection. Metastatic liver disease was initially classified according to the classification of Gennari et al.[19] Table 2 lists the distribution by extent of liver involvement and multiplicity of metastases. This classification provided the basis of a subsequently developed staging system[20] in which different cases were grouped according to a shared prognosis. Case distribution within different stages and the type of surgery performed are reported in Table 3.

Postoperative examinations, including clinical examination, carcinoembryonic antigen (CEA) test, liver function tests, and sonography or isotope scan, were performed every 3–4 months. Barium enema or endoscopic examination, liver CAT, and chest x-ray were performed twice yearly. Unless patients complained of specific symptoms, bone x-ray, total abdomen CAT, and brain scan were not routinely performed. Median postoperative follow-up was 18 months (range: 4–45 months).

Life table analysis was used to calculate survival rate, and statistical significance was evaluated according to the Mantel-Haenszel test.[21]

Results

After a median follow-up of 18 months (range: 4–45 months), 28 patients (62%) had a relapse. The recurrences were only hepatic in 11 patients (39%), only extrahepatic in 12 patients (lung, 17%; pelvic, 21%; brain, 3.5%), and both hepatic and extrahepatic in five patients (18%). The relation between rate and site of recurrence and some characteristics of the metastases is reported in Table 4. It appears that the most important factors in determining the overall recurrence rate were stage, number of metas-

TABLE 4. *Patterns of Failure After Hepatic Resection (Median Follow-up, 18 Months)*

Characteristics of Metastases	No. of Patients	Hepatic Relapse*	Distant Relapse			Total*
			Intra-abdominal*	Extra-abdominal*	Distant and Hepatic Relapse*	
Colon	33	8 (24)	2 (6)	5 (15)	4 (12)	19 (57)
Rectum	12	3 (25)	4 (33)	1 (8)	1 (8.5)	9 (75)
Single	26	4 (15)	4 (15)	4 (15)	2 (7.6)	14 (53)
Multiple	14	5 (35)	2 (14)	2 (14)	2 (14)	11 (78)
Bilateral	5	2 (40)	—	—	1 (20)	3 (60)
$H_1 \leq 25\%$†	27	5 (18)	4 (14)	2 (7.4)	3 (11)	14 (51)
H_2 25–50%	10	1 (10)	2 (20)	3 (30)	1 (10)	7 (70)
$H_3 > 50\%$	8	5 (62)	—	1 (12.5)	1 (12.5)	7 (38)
Stage I	21	3 (14)	4 (19)	2 (9.5)	1 (4.7)	10 (47)
Stage II	8	2 (25)	—	1 (12)	2 (25)	5 (62)
Stage III	16	6 (37)	2 (12)	3 (18)	2 (12)	13 (81)
Total	45	11 (24)	6 (13)	6 (13)	5 (11)	28 (62)

* In parenthesis, percentage.

† Percentage of hepatic involvement.

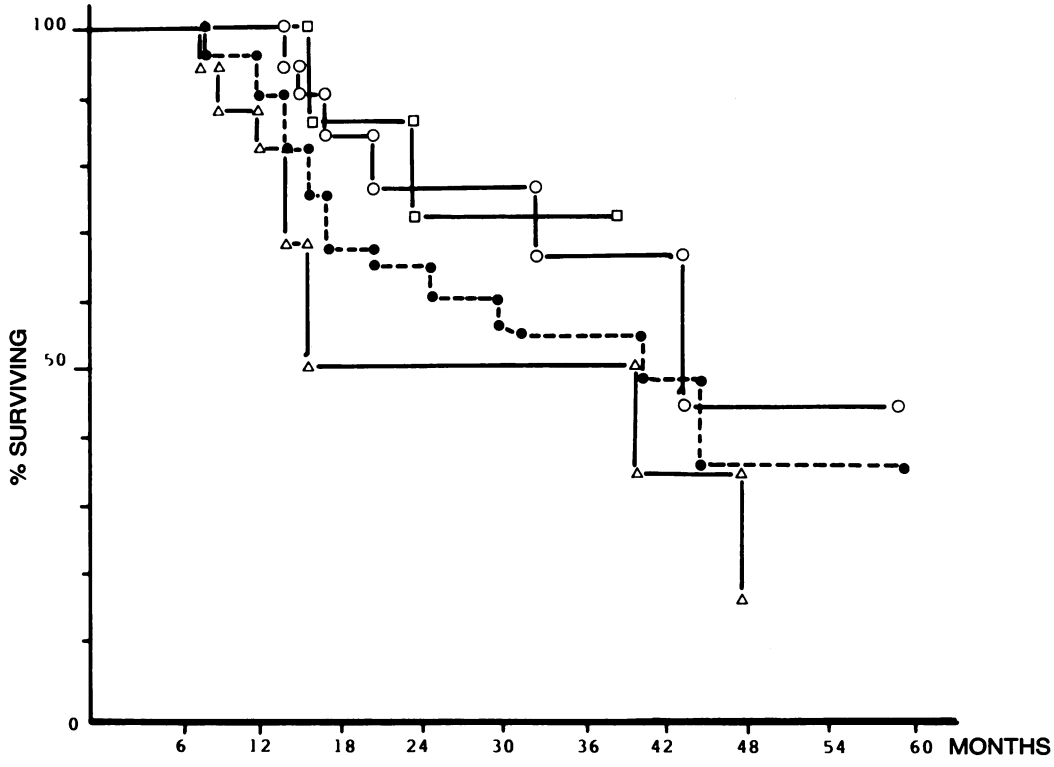

FIG. 1. Actuarial survival by stage: ○, stage I (21 patients); □, stage II (8 patients); △, stage III (16 patients); ●, overall (45 patients).

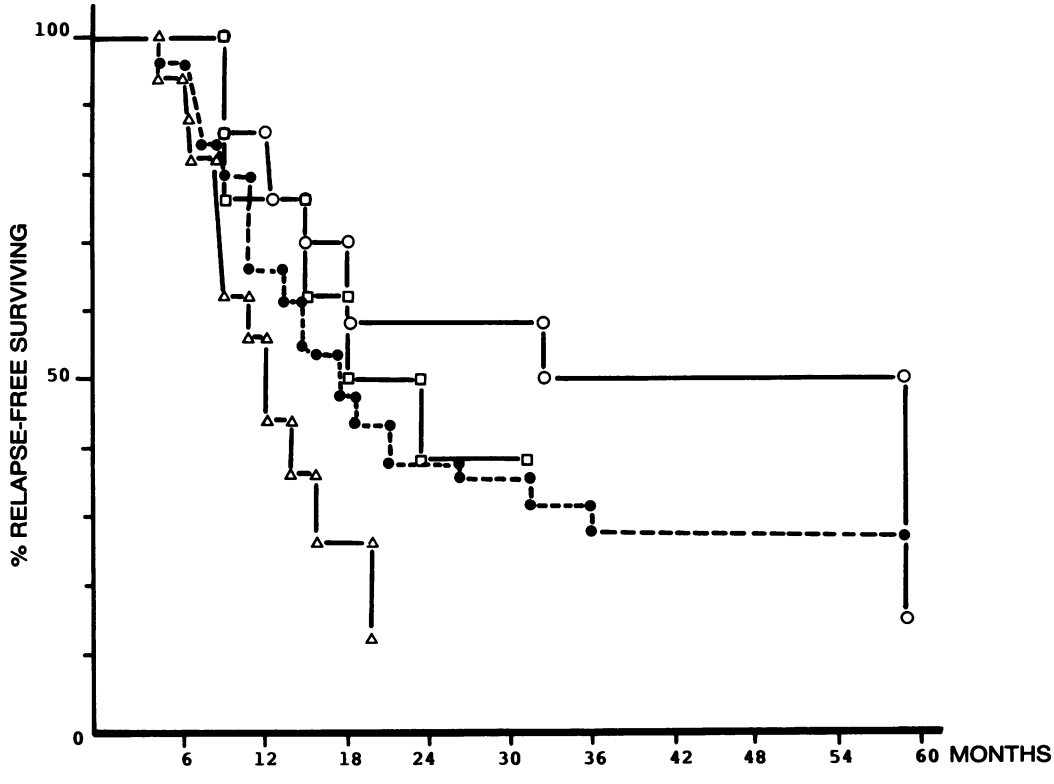

FIG. 2. Actuarial relapse-free survival by stage: ○, stage I (21 patients); □, stage II (8 patients); △, stage III (16 patients); ●, overall (45 patients).

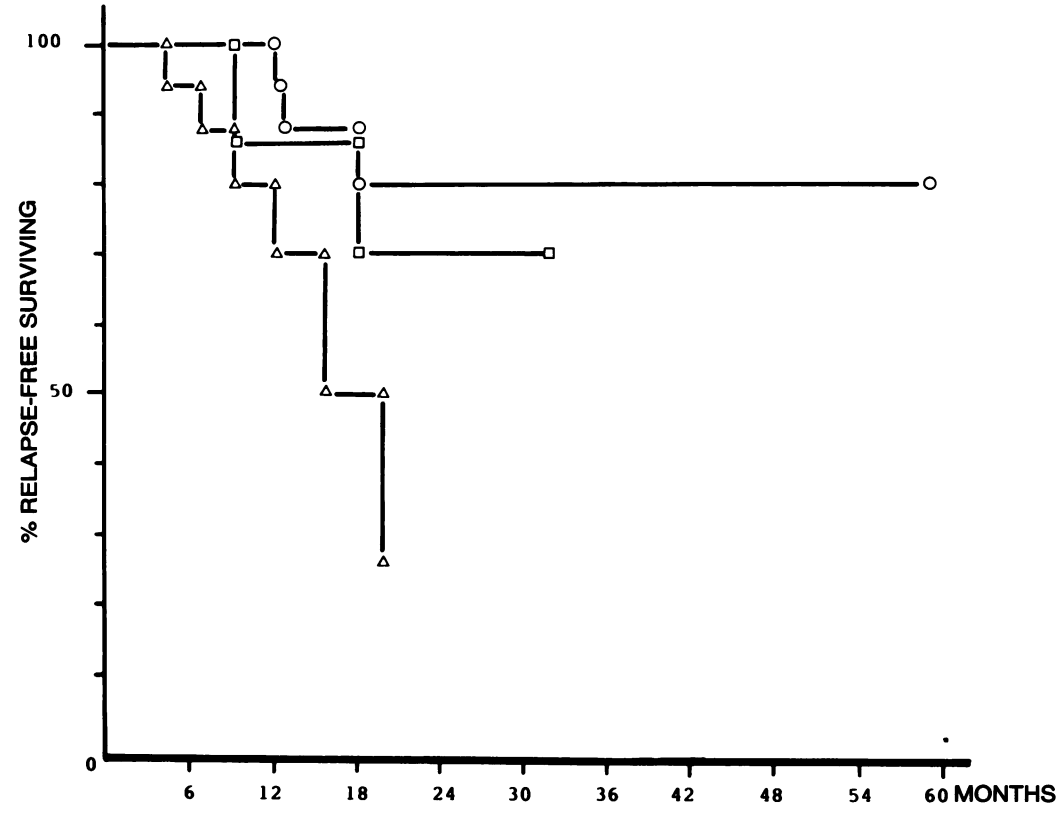

FIG. 3. Hepatic relapse-free survival by stage: ○, stage I (21 patients); □, stage II (8 patients); △, stage III (16 patients).

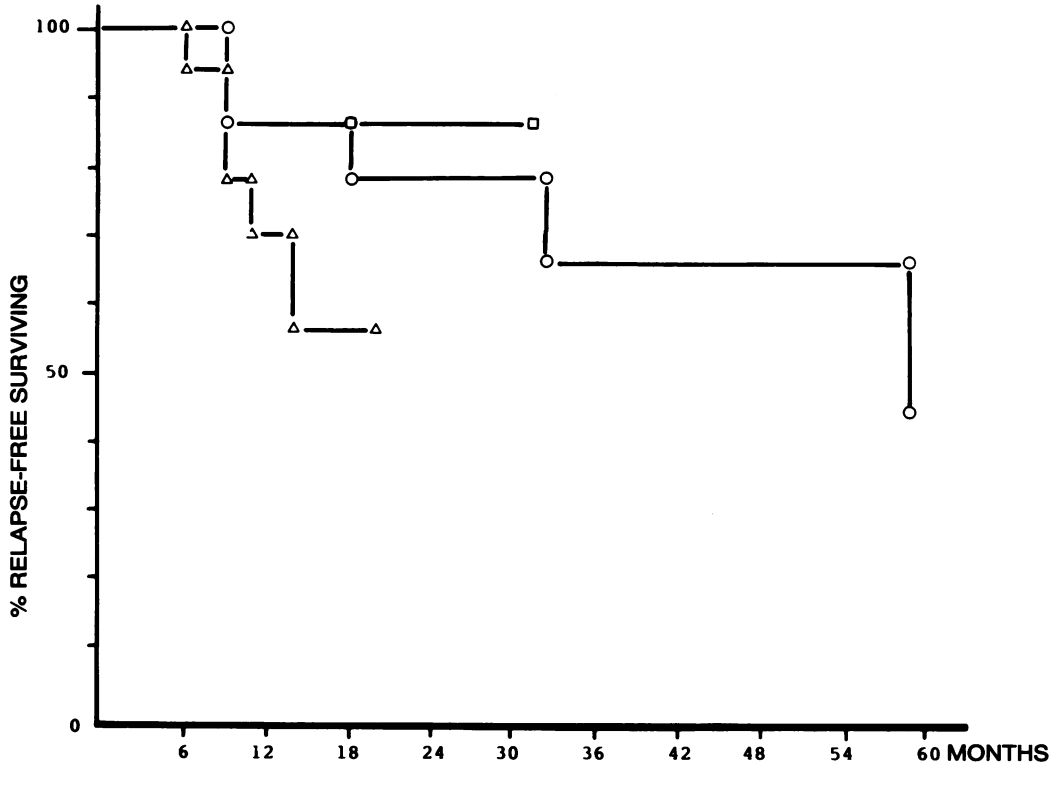

FIG. 4. Extrahepatic relapse-free survival by stage. ○, stage I (21 patients); □, stage II (8 patients); △, stage III (16 patients).

TABLE 5. *Areas of Failure After Liver Resection (Review of the Literature)*

Authors	Year	No. of Patients	Site of Failure		
			Hepatic	Extrahepatic	Both
Rajpal et al.[5]	1982	30			11
August et al.[17]	1984	33	11	9	
Fortner et al.[13]	1984	37*	5	10	2
Nims[18]	1984	9		1	2
Steel et al.[16]	1984	30	3	9	1
Cady & McDermott[1]	1985	23	7		
Petrelli et al.[11]	1985	36	2	4	11
Butler et al.[8]	1986	62	10		10
Current series	1986	45	11	12	5
Total		305	49 (16%)	45 (14.7%)	42 (13.7%)

* Only stage I patients according to the authors' classification.

tases, and extent of liver replacement. There was a high recurrence rate of distant metastases when the primary tumor was in the rectum (75%), and pelvic relapses accounted for 33% of them. When site and rate of relapses were related to other variables (synchronous *vs.* metachronous, type of surgery, preoperative CEA, Dukes' classification and grading), no statistical relationship was found.

The median interval between liver resection and hepatic and extrahepatic recurrence was 9 and 10 months, respectively. Predicted overall and relapse-free survival, overall and by stage, are reported in Figures 1 and 2. Hepatic and extrahepatic relapse-free survival rates are reported in Figures 3 and 4, respectively. The risk of developing a hepatic relapse after 18 months was 20% in stage I, 31% in stage II, and 50% in stage III. The relapse rate by stage was significantly different ($p = 0.01$). The risk of developing an extrahepatic recurrence after 18 months was 23% in stage I, 14% in stage II, and 44% in stage III. The difference was not significant. However, considering the cumulative rate of hepatic relapse (alone or associated with an extrahepatic recurrence), significantly different curves were observed by stage ($p = 0.01$) 18 months after surgery with values of 26% in stage I, 43% in stage II, and >50% in stage III. In contrast, the cumulative rate of extrahepatic metastases (alone or associated with hepatic recurrence) was not affected by stage. In fact, at 18 months after surgery the curves and values of 28% in stage I, 28% in stage II, and 51% in stage III were not significantly different. According to stages I, II, and III, median recurrence times for hepatic and extrahepatic relapses were, respectively, 12, 10, 10 and 12, 6, 7 months.

To evaluate the role of liver resection on the subsequent onset of hepatic relapses, 16 cases of hepatic recurrence after resection were analyzed. Relapses were confined to the bed of resection in only four of these cases (25%), and in the remaining 12 cases the relapses were unrelated to the site of resection and were disseminated throughout the parenchyma. One of the four cases was classified as stage I, one as stage II, and two as stage III. In two cases the metastases were single, and in two cases they were multiple or bilateral. The surgical procedures adopted were sublobectomy (2 cases), right lobectomy (1 case), and extended right lobectomy (1 case).

Discussion

The analysis of the patterns of failure after hepatic resection for metastatic colorectal cancer showed that areas of failure included the liver, intra-abdominal extrahepatic structures, and extra-abdominal organs. Our data further complement the scanty information in the literature (Table 5). The discrepancy between our data and those from the literature probably reflects some difference in methodology of follow-up and statistical analysis of the data. Furthermore, the information was scattered in the quoted papers; only one of them[16] was directly addressed to evaluate the patterns of recurrence. The most frequent extra-abdominal site of failure was the lung (17% of all relapses), whereas the intra-abdominal extrahepatic spread of the disease (13% of all relapses) involved retroperitoneal nodes (1 patient), the operative bed (anastomosis in 2 patients and pelvis in 4 patients) and the peritoneum. This fact suggests that an intraoperative evaluation should be very careful and meticulous even when a negative CT scan or magnetic resonance imaging indicates that the disease is confined to the liver, especially when the primary was in the rectum.

The frequency of hepatic recurrence, alone or in association with other sites, was related to the stage, whereas the rate of extrahepatic relapse was unaffected by stage.

The stage I failure rate at 18 months was approximately equal for hepatic and extrahepatic relapse (occurring in one third and one fourth of the patients, respectively), whereas in stages II and III the hepatic relapse rate was always higher than the extrahepatic rate. It is not surprising that the relapse rate in the liver was related to stage. In fact, the stage was determined by the size and number of metastases present. The larger the tumor and the greater the number of nodules present, the higher the risk that multiple neoplastic foci will remain undetected by the surgeon during liver resection. In contrast, in patients with limited or extensive liver metastases, microscopic tumoral foci may be present in the lung several years before diagnosis of the primary.[22]

An interesting question is whether hepatic recurrence after liver surgery is due to an incomplete resection or to surgical manipulation. Since the reported doubling times of liver metastases range from 50 to 112 days[23,24] (a much higher figure than the corresponding colon carcinoma doubling times of 53–620 days), further speculation regarding the development of new metastases may be made. If a detectable tumor measuring 1 cm^3 is composed of approximately 10^9 cells and reaches such a size after 10 doublings of a tumor measuring 1 mm^3 (10^6 cells), a liver metastasis detected after a 10-month interval (after 2–5 doublings) is hypothetically due to a gross neoplastic residue within the liver or an extremely accelerated postoperative growth rate, or both. However, it is not likely that this is due only to the operative spread of neoplastic cells, which should exceed 10^6 in number. It should also be considered that, at least in experimental tumors, the surgical stimulus on the growth and kinetics of a residual tumor is believed to last only a few days.[25,26] Since the median interval for the onset of lung metastases is very similar to that of hepatic recurrence, it is apparent that spread to the lung occurs in a very early phase of the disease.

These data demonstrate that after failure of surgery on a primary tumor of the large bowel, a second "local" approach on liver metastases will fail in a high percentage of patients, and the disease will recur in the liver and in extrahepatic sites. To improve survival, an adjuvant therapy covering potential areas of future relapse in the liver, abdomen, and distant sites is probably warranted in a phase in which limited (microscopic) disease could be present. Since only a few liver relapses after liver surgery were confined to the operative bed (25%), and liver relapses alone accounted for 39% of overall relapses, it appears that the potential benefit of an "extended" surgery may be derived by less than 10% of the patients according to our experience, and 4% according to the cumulative series of the literature.

Owing to this limited therapeutic potential, a new *de principe* extended surgical approach, including right lateral sectoriectomy for metastases located in segments VI and VII, a left lateral lobectomy for tumors of segments II and III, or a portal guided resection under intraoperative sonographic control,[27] should be done only if minimal morbidity is warranted. In contrast, recent data[28] have shown that intraperitoneal administration of 5-fluorouracil achieves a portal venous level 10–40 times higher than that of intravenous dosing, and furthermore that the development of peritoneal carcinosis can be partially prevented. Therefore, a course of intraperitoneal 5-fluorouracil or fluorodeoxyuridine[29] should probably be alternated with systemic therapy, which alone did not prove successful after liver surgery.[30] In this context, the use of systemic intravenous fluorodeoxyuridine should also be taken into consideration.[31]

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